Why do individuals agree to enrol in clinical trials? A qualitative study of health research participation in Blantyre, Malawi

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Abstract

Current literature suggests that therapeutic misconception – a belief by participants in a clinical trial that they are in fact simply being given clinical care – is common, especially among illiterate populations in developing countries. Therapeutic misconception reflects problems in informed consent, as people agree to participate in clinical trials without being aware that the trial procedures and test products may not in fact benefit them.

In this study of Malawian adults who had participated in research projects of various kinds during the preceding years, we found that the majority participated in research for the sake of obtaining better quality treatment made available through the clinical trials as ancillary care. Their consent to participate was not due to a belief that the actual procedures of the trial would directly benefit their health. Respondents indicated that, government hospitals being crowded and commonly lacking drugs, they agreed to take part in research projects in the hope of obtaining access to ancillary care provided by clinical trials.

We conclude that in this environment, possibly owing to inadequacy of routine health services, people make rational decisions to participate in research. We question whether the term 'therapeutic misconception' accurately describes participants' motivation under conditions of limited resources. We also discuss the relevance of these findings for understanding undue inducement in clinical trials.

Introduction

Health research presents several unique ethical challenges in developing countries such as Malawi. One of the major ethical challenges that has been identified in studies conducted elsewhere is that of research participants confusing medical research with routine medical care. This challenge is referred to as a *therapeutic misconception* and is defined as a mistaken belief by trial participants that they are participating in research only for the sake of being treated and not for the sake of generating or obtaining new information. Appelbaum, Roth and Lidz first described "therapeutic misconception" in 1982. [1] Since then, several studies have been conducted in order to investigate its existence and prevalence among clinical trial participants. Some studies have sought to understand why it exists while others have sought to understand the role of investigators in its genesis. [2,3] Other related studies have sought to establish the understanding of people who agree to participate in trials. To date, several authors have reported the difficulties that researchers face in describing the concepts of research, randomization, placebo use and double blinding to trial participants. [4-10]

A therapeutic misconception occurs when a research subject transfers to the research setting the assumption that the physician always acts only in the best interests of the patient. [11] In research, there are procedures such as randomisation, placebo use and double blinding that challenge this assumption. These three major scientific procedures that separate clinical trials from routine health care pose challenges to one of the principles of ethics, namely beneficence – the obligation to do good. According to this principle, the researcher is obliged to act in a way that benefits the wellbeing of the research participant. The researcher is bound to maximize the chances of a successful outcome.[12] As a result of a therapeutic misconception, research participants do not consider that they are going to be randomized to various groups, that there is a chance that they may receive a placebo, that a placebo does not contain the active ingredient, that the purpose of the research is to test the product or intervention or that even the researchers or research staff do not know whether they are giving individual participants the placebo or the active product or intervention. For the investigator whose research involves patient care, ethical requirements governing the provision of that care must, of course, still prevail. But the investigator has additional obligations to ensure that the study or trial is soundly accomplished.

According to Appelbaum, on average 70% of trial participants in clinical research suffer from a therapeutic misconception. [13] Some papers have suggested that therapeutic misconceptions are particularly prevalent among research participants in African populations that are characterized by low literacy levels.[14,15]

Miller and Brody note that the two activities, medical research and treatment are fundamentally different and require different ethical approaches. In clinical care, the ultimate goal is to provide therapy to the individual.[16] Thus any new knowledge gained is incidental to the main aim of the activity. By contrast, the goal of clinical research is to generate new knowledge that can help future patients. Failure to distinguish the consequences of research participation from receiving ordinary treatment may seriously undermine the informed consent of research subjects. Brody observes that a therapeutic misconception is a major practical problem in medical research even in developed countries and suggests that researchers and bioethicists have to find some ways of eliminating it.[17] Brody considers that the therapeutic misconception results primarily from an overlap between the role of the attending physician and the role of the investigator in a research trial. This overlap is greatest when the same physician occupies both roles with respect to a particular patient-subject. With therapeutic misconception,

participants enrol in research without being aware of the personal implications of their participation.

In this paper we report findings relevant to therapeutic misconception from the first qualitative phase of a three-year study of clinical research taking place in Blantyre, Malawi. The purpose of the overall three-year study is to understand participants' perceptions, understanding and attitudes towards health research. The work presented in this study is from the first phase, aimed at gathering information on concepts and terminology in preparation for subsequent phases: Phase 2 will be informed by Phase 1, but will be quantitative and will focus on participants of selected clinical studies.

Study setting

The study was carried out by a team from the Center for Bioethics in Eastern and Southern Africa (CEBESA) within the Department of Community Health at the College of Medicine, University of Malawi. The College of Medicine in Blantyre is associated with many research programmemes, some in collaboration with the Malawi-Liverpool-Wellcome Trust Clinical Research Programmeme, the Johns Hopkins University Research Centre, the University of North Carolina Research Centre, the Gates Foundation supported Malaria Alert Center, and the University of Michigan Blantyre Malaria Project. This institutional base puts the team in a strong position to conduct research in ethics related to past and ongoing clinical research. The qualitative study was conducted in three locations in Southern Malawi, namely the rural settings of Madziabango and Mpemba Health Centre catchment areas located in Traditional Authority Somba in Blantyre District and the urban location of Bangwe Township within Blantyre City. These locations were selected for the qualitative study because several medical research projects had been and are still being conducted there. Bangwe is a ward within Blantyre City with a recorded population of 35,729 (8,761 households) according to the 1998 population census; 14% of this was under 5 years and 39% under 15 years old. It is one of the most densely populated wards of Blantyre City with more than 3,200 persons per sq. km. The mean maximum educational level in households is 7-9 years which is above the national average of 5.6 years. [18] Bangwe ward has a government health centre, primary schools (private and government), Faith Based Organizations, and several Non Governmental Organizations. At the time of this study, the following projects were either completed or were underway in the area:

- Since January 2003 University of Malawi's College of Medicine (COM) and Salvation Army, a faith based organization, have been carrying out a home based care and nutrition programme for people living with HIV/AIDS. Every year, first year medical students conduct demographic surveys among the project clients in fulfilment of their community health curriculum.
- The Johns Hopkins Research Centre was running a study focused on the prevention of mother to child transmission using Nevirapine. Participants are HIV positive mothers and their newborn infants. The study is ongoing.
- The Wellcome Trust funded the Azithromycin for Prevention of Preterm Labour Study (APPLE), focusing on infections in pregnancy and premature deliveries was also going on in the area.

The rural communities of Mpemba and Madziabango lie southwest of Blantyre city, along a tarmac road (Blantyre-Chikwawa road). Both are within Traditional Authority Somba, Blantyre District. The population of Mpemba and Madziabango are mainly subsistence farmers who grow chiefly maize, but who also cultivate cassava and vegetables and keep chickens. Health institutions in TA Somba include Mpemba and Madziabango Health Centres. At the time of this study, the following institutions had either completed studies or had studies underway:

- University of North Carolina and College of Medicine's Department of Community Health had conducted a study focusing on prevention and control of malaria in pregnancy. Participants were pregnant women who delivered at the health centres. The study was conducted between April 2002 and November 2003. Follow up was being done at the time of this study.
- Population Services International, distributors of bed nets, is carrying out ongoing operational research since November 2004. Three types of bed nets were being compared and everyone can participate.
- The Gates Malaria Alert Centre is running a Drug Revolving Fund where village health committee members are being given malaria drugs to sell in the communities.
- An infant nutritional study [Mpemba only] is being carried out by an NGO called GOAL.

Study methods

Ethical approval was sought from the College of Medicine Research and Ethics Committee (COMREC), additionally Blantyre District Health Officer (DHO) approved for the research to be conducted in Bangwe, Madziabango and Mpemba government health centers. Through the Nursing Sister and Clinical Officers-in-Charge at each health centre, the local Health Surveillance Assistants (HSAs) were then approached to mobilize community members. HSAs were called upon to assist in arranging the focus groups because of their familiarity with people living in the study communities. They approached both male and female community members and enquired whether they had participated in health research during the past three years or were currently participating in clinical studies. Those who confirmed and showed interest were invited to participate in the focus group discussions. After explaining the study, oral individual consent was obtained from each of the respondents. The respondents were also asked to give their permission for audio-taping of the discussion. All the focus group discussions occurred in a private place in both settings. Each respondent was assigned a unique identification code and individual responses were represented by identification codes.

Using this process, eighteen focus group discussions were held with 182 participants (76 rural; 106 urban) who were participating or had previously participated in health research.

Each focus group was composed of 6-12 people; of whom 13% were male and 87% female. This unequal gender distribution was due to the fact that most of the studies conducted in the three sites involved women and children.

All focus group discussions were conducted in Chichewa and were recorded on audiotapes, which were then transcribed manually and translated from Chichewa into English by members of the research team. The number of discussions was balanced between the rural and urban sites to allow for comparison; 9 focus groups were conducted in each setting. Table 1 shows the various FGDs that were held.

Table 1: Summary of Focus Groups

Location	No of Focus groups	Male	Female
Rural	9	21	84
Urban	9	2	75
Total	18	23	159

Results

Descriptions of research studies

Participants were asked to describe the studies that they have participated in, they described 14 studies .

Two observations are noticeable of the programmes mentioned by the participants. Firstly, not all programmes mentioned by the research participants were clinical trials, nor were they health research projects of any other kind, but were in fact standard health care interventions. A few participants thought other routine health services, such as family planning, bilharzia screening, vaccinations against polio and measles, vitamin A administration, distribution of chlorine to prevent cholera, distribution of mectizan against black flies, TB screening, education and treatment, were health research in the local areas. That these health care provision programmes were thought to be research projects represents the inverse of therapeutic misconception, which we might term 'research misconception'.

Secondly, this problem makes it difficult to gather to what extent there is a therapeutic misconception among people who took part or were taking part in a research study. We would expect a therapeutic misconception to manifest most in hospital based clinical trials, but participants were involved in a range of health programmes and research activities, making the descriptions and understandings difficult to disentangle. Furthermore, the intervening period between their taking part in research and the time the FGDs may have led to recall bias. The question of how pervasive the therapeutic misconception is cannot therefore be answered here and must be more thoroughly tackled in the second phase.

What is research?

Given the responses reported and issues raised above, one of the most important questions asked during the FGDs is the respondents' understanding of the term "research". The majority of the participants had an idea that research was about trying to find out about something. Respondents from rural and urban areas came up with the same Chichewa expressions defining what research is. All the terms suggest the idea of "finding out" about something. Below are the recurring Chichewa expressions given by the respondents:

- *Kufufuza/kuwunguzawunguza/kufunafuna:* to investigate
- *Kusakasaka*: hunting for something.
- *Kalondolondo*: to follow up on something.
- *Kusanthula/kuwunika*: to illuminate.
- *Kalembera*: a census.

Health research was seen by many peri-urban and rural respondents as investigating outbreaks of diseases, establishing why they are occurring, and devising ways of preventing their spread:

> *"My understanding is that health research involves investigating a disease; to find out why the disease has come about, how to prevent it in case it has no cure, as well as how to find a cure for the disease."* (P5, FGD36, Participants - urban)

Health research was also perceived to be diagnostic in nature: blood is drawn from participants to determine the cause of a disease; the number of cases is quantified and the population requiring assistance identified.

> *"According to me, my opinion is that when there is a wide spread disease among the people, whether it is malaria or HIV/AIDS, they (researchers) endeavor to investigate the cause of the disease."* (P10, FGD33, Participants - urban)

Health research was viewed by some as a way of trying out the efficacy of new drugs. This view was common among respondents.

> *"They wanted (researchers) to find out what he/she was suffering from and they were also trying a new drug for treatment"* (P10, FGD37, Participants - urban)

The above quotes illustrate the complexity of teasing out whether the investigations are part of a systematic effort to produce new knowledge for the benefit of the general population in the future (how we are defining research), or whether they were carried out as part of health surveillance, health provision or public health initiatives.

Why join studies?

In order to understand the role of a therapeutic misconception in study participation, we interviewed participants who reported being aware that they were in studies to test the efficacy of certain drugs or interventions. We asked them why they decided to participate. What clearly emerged was the fact that the desire to seek medical treatment overrode the primary intent of health research. Participants revealed that they often chose to participate in research so as to obtain better treatment. Public hospitals are always overcrowded and short-staffed, and are characterized by long waiting hours, while private hospitals are very expensive. Respondents characterized normal health care in health centres as inadequate; medication is given without proper diagnosis, and the range of medications available is often severely limited.

In health research, by contrast, participants perceive that treatment is prompt and is given after a proper diagnosis (screening of blood, urine etc); hospitalized patients are

given good food and are sometimes discharged home in a project car. They are even followed up at a later stage in their homes. Most of the clinical trials associated with the College of Medicine offer treatment free of charge even for other problems not related to the study ('ancillary care'), and people do not have to wait for hours since clinical trials are often adequately staffed.

The views of this participant embody this perception:

> *"…when you are taking part in research, they treat you differently from those who are not taking part in research. For example, if you are suffering from some illness and you explain to the doctor that you are a research participant, they try hard to give you all the care needed. But if you are not a participant, they can just give you aspirin and you go".* (P5, FGD no.39)

Differences between health research and routine health care:

Given the overlapping descriptions of health research and routine health care, we also asked participants to describe the key differences between the two. Many respondents cited quality of care as a major distinguishing factor between health research and health care. Thus in health research, treatment and care is considered better than in normal health care. When hospitalized, they even provide good food:

> *"When you take part in health research, the reception you are accorded is very warm and you are free to reveal all your worries according to your health problem. But when you go to government hospitals, once you name your major complaint, it ends there. There is no room for additional complaints."* (P5, FGD34, Participants - urban)

In health research, investigators even make follow ups at your home:

> *"In a health study, after giving the patient medication they even make follow ups at the home of the patient to monitor her progress. When other patients receive normal care at the hospital that is the end of it."* (P7, FGD17, - rural)

The majority of participants perceived the care that was offered through research projects as adequate and correct i.e. it is based on thorough diagnosis, unlike that which is offered through routine care which is mainly based on oral history only. Thus, diagnosis was perceived not to be thorough in 'normal' treatment.

> *"You may go to the hospital tell them you are suffering from headache or fever. They just prescribe the medicine for you for fever. They do not screen you. While when you go to a health research, they screen you first to find out exactly what the problem is. Soon after diagnosis, you are given medicine."* (P5, FGD44, Participants - urban)

An additional commonly cited difference was that in health research, people can take part even if they are not sick which is not the case with health care:

> *"The difference is that we get medical treatment when we are sick while in research you are given all sorts of assistance even if you are not sick."* (P4, FGD4, urban).

This comment is rather different from the previous ones. One possibility is that research is sometimes considered to be a form of aid, or that it is linked to special health provision where illnesses are handled preventatively.

Discussion

From the recorded comments of the respondents in this study, it was evident that the majority had chosen to participate in a research project as a way of accessing better quality health care, while knowing that the primary purpose of the project was a research investigation. In a situation of poor service delivery as is the case in Malawi, research programmes commonly offer access to health care that is quicker, more comprehensive and more personal than is available in national medical facilities. Some respondents described visits to the hospital during which they spent several hours in the queue only to be told that there were no drugs for their problem.

The findings lead us to ask the question: is it reasonable, ethically justifiable, and acceptable to offer, as a benefit of participation in a research project, better quality general health care than is available through the local health services? Or does such research in limited resource settings carry with it an undue inducement? We are of the opinion that if people make an autonomous decision to join health research, then permitting them to join with the principal motivation of improving their health care is not unethical.

The issue of undue inducement becomes important only if one does not consider the risks of participation. In most cases, the decision to participate in research was out of perceived self-interest, with the main reason that of promoting health rather than the pursuit of other material benefits. In a scenario where the national health delivery system is overburdened and fails to adequately respond to individuals' health needs, individuals will take the best available option, which may be to enrol in a research study. We view this decision as a rational one, because it is made after considering the advantages as well as the costs of deciding not to join the study on offer. Of concern though, is the fact that the participants place more importance on the benefits associated with participation. It is not clear whether participants considered the risks associated with participation such as possible side reactions or bodily injury. It is possible that research team members may play an important role in contributing towards the failure to consider risks, by placing more emphasis on benefits at the expense of risks.

In the context of the present inquiry, the overcrowded government hospitals and the expensive private hospitals are perhaps more correctly identified as constituting coercive circumstances than the research programmes. In limited resource settings such as those prevailing in Malawi, research plays an important role that has not yet been fully acknowledged. Research complements the national delivery systems which are overburdened. By complementing local delivery systems, research is indirectly contributing – albeit in relatively small pockets - to the redistribution of resources to poor communities. At the same time the potential harmful impact of the research on the routine health services should be assessed and mitigated so that others in the community do not suffer as a consequence of the research.

Therapeutic misconception in Malawi

How prevalent and how important is therapeutic misconception in the communities we have studied? We believe that the term is context specific and that caution needs to be exercised in using it, particularly in resource limited

settings. A therapeutic misconception can be found in any situation in which it is difficult to tell the differences between routine care and clinical research. In resource limited settings patients often judge the difference between research and routine care based on the quality of care. In many cases this is a reflection of the relatively large resources made available to research programmes operating in resource constrained environments.

For the term therapeutic misconception to fit a particular situation, there should be a mistaken belief on the part of the patient that the research is aimed simply at treating their current disease. A rational decision by someone to participate in a trial for the sake of accessing better quality health care in general does not qualify for that label, except when he believes that the intervention itself is designed to benefit him and does not understand the possibility of being allocated to a control arm. Therapeutic misconceptions, therefore, can be divided into two types: participants thinking that the research is normal (relatively good quality) health care, or thinking that it is research and assuming that the research intervention has individual benefit. We believe that what we have observed in our study is less likely to be one of these forms of therapeutic misconception, and more likely to be the push and pull effects associated with limited resources. Our Phase 2 research will test this idea.

Do these findings indicate that the participants whose opinions we report have joined research projects because of undue inducement? In our view this is not the case. Our findings relate to people who are capable of making decisions to promote their own health. Research in African and other resource-limited countries plays an extra role that is yet to be fully acknowledged. The appropriateness of the term therapeutic misconception in a situation of poor public health care has been questioned previously [19], and our study underlines this concern.

Conclusion

Therapeutic misconception has been observed in many resource poor settings, as a result of many factors including the difficulty experienced by researchers in explaining research concepts in such a way that participants adequately comprehend them[4,5,7-10,13-15]. In the communities we describe, the therapeutic misconception does not appear to have been a feature of people's participation in research. Respondents were aware of the investigative nature of the studies in which they took part, and they participated in order to benefit from the superior general health care to which the research gave them access. We argue, with others, that this is a reasonable and ethically acceptable motivation for taking part in research and does not constitute therapeutic misconception. This provision of general and ancillary health services to research subjects does, however, require careful planning and monitoring to ensure that it does not lead participants, in their pursuit of better clinical care, to ignore the potential risks of being involved in research.

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